

Application S. No. 10/762,444  
Filed: January, 21, 2004  
Page 9 of 15

#### REMARKS

Claims 1-6 and 8-11 are pending after entry of this amendment. Claim 7 is cancelled. Claims 1, 4, 8 and 9 are amended. Applicants reserve the right to file divisional/continuation applications to the cancelled subject matter.

Claims 1, 4 and 9 are amended, in part, to conform with the restriction requirement. Basis for the amendments can be found in the application. For example, the amendment to incorporate the definition of non-interfering substituents finds basis in the specification on page 15, line 30 through page 16, line 2. No new matter is added.

#### CHANGE OF CORRESPONDENCE ADDRESS

Applicants request that PTO records be updated to reflect the change in correspondence address in the instant case. A request for the Change of Correspondence Address was submitted on September 28, 2005. Copies of the request and the return receipt are attached.

#### REJECTION OF CLAIMS 4-8 UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 1-11 are rejected under 35 U.S.C. §112, second paragraph, for allegedly being indefinite. The Office Action alleges that the expression "non-interfering substituents" fails to clarify the intended meaning.

Applicants respectfully submit that the claims are amended herein to incorporate the definition of the phrase "non-interfering substituents" from the specification. Reconsideration and removal of this rejection is requested.

#### REJECTION OF CLAIMS 4-8 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH FOR ALLEGED LACK OF ENABLEMENT

Claims 4-8 are rejected under 35 U.S.C. § 112, first paragraph because the specification, while being enabling for certain disorders characterized by  $\alpha$ -synuclein, allegedly does not reasonably provide enablement for all disorders characterized by  $\alpha$ -synuclein. The Office Action alleges that the specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims. Applicants respectfully request reconsideration and removal of this rejection in view of the amendments and remarks herein.

#### Relevant Law

To satisfy the enablement requirement of 35 U.S.C § 112, first paragraph, the specification must teach one of skill in the art to make and use the invention without undue

Application S. No. 10/762,444

Filed: January, 21, 2004

Page 10 of 15

experimentation. *Atlas Powder Co. v. E.I. DuPont de Nemours*, 750 F.2d 1569, 224 USPQ 409 (1984). This requirement can be met by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything *within the scope* of a broad claim." *In re Anderson*, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. Rather, the requirements of § 112, first paragraph "can be fulfilled by the use of illustrative examples or by broad terminology." *In re Marzocchi et al.*, 469 USPQ 367 (CCPA 1971)(emphasis added).

Further, because "it is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species, it is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it." *In re Grimme, Keil and Schmitz*, 124 USPQ 449, 502 (CCPA 1960). Thus, there is no doubt that a patentee's invention may be broader than the particular embodiment shown in the specification. A patentee not only is entitled to narrow claims particularly directed to the preferred embodiment, but also to broad claims that define the invention without a reference to specific instrumentalities. *Smith v. Snow*, 294 U.S. 1, 11, 24 USPQ 26, 30 (1935).

Applicant is entitled to claims are commensurate in scope not only with what applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicant has disclosed.

The inquiry with respect to scope of enablement under 35 U.S.C. §112, first paragraph, is whether it would require undue experimentation to make and use the claimed invention. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int'l 1986); see also *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

Application S. No. 10/762,444  
Filed: January, 21, 2004  
Page 11 of 15

### **Analysis**

Applying the above factors to the instant claims, applicants respectfully submit that, as described in detail below, it would not require undue experimentation to practice the full scope of the claimed subject matter.

### **Scope of the claims**

Applicants respectfully submit that claim 4 is directed towards methods for treating Lewy body disease or Parkinson's disease using a compound of formula A. Claims 5, 6 and 8 depend from claim 4 and further define the method. The compounds used in the methods of the instant claims are described in detail in the application (see, e.g., page 8, line 15 through page 11, line 3; page 12, line 1 through page 14, line 7; and page 17, line 27 through page 18, line 25). The application describes Parkinson's disease and  $\alpha$ -synuclein fibril formation, see, e.g., page 7, line 9 through page 8, line 12. Therefore, the scope of the instant claims is not broader than the application disclosure.

### **The level of skill in the art is high**

The level of skill in this art is recognized to be high (see, e.g., *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int'l 1986)). In addition, the numerous articles and patents that are of record in this application that are authored by those of a high level of skill for an audience of a high level of skill further evidences the high level of skill in this art.

### **Knowledge of those of skill in the art**

At the time of the effective filing date of this application and before, one of skill in the art knew the role of  $\alpha$ -synuclein fibrils in Lewy body disease and Parkinson's disease. The articles cited in the specification and of record, describe the role of  $\alpha$ -synuclein fibrils in these diseases. For example, at the time of the effective filing date of this application and before, a skilled artisan was aware that Parkinson's disease is a neurodegenerative disorder that is pathologically characterized by the presence of intracytoplasmic Lewy bodies (Lewy in *Handbuch der Neurologie*, M. Lewandowski, ed., Springer, Berlin, pp. 920-933, 1912; Pollanen et al., *J. Neuropath. Exp. Neurol.* 52:183-191, 1993). Further, it was known that the major components of Lewy bodies are filaments consisting of  $\alpha$ -synuclein (Spillantini et al., *Proc. Natl. Acad. Sci. USA* 95:6469-6473, 1998; Arai et al., *Neurosci. Lett.* 259:83-86, 1999), an 140-amino acid protein (Ueda et al., *Proc. Natl. Acad. Sci. USA* 90:11282-11286, 1993). As described by

Application S. No. 10/762,444

Filed: January, 21, 2004

Page 12 of 15

described by Polymeropoulos *et al.*, two dominant mutations in  $\alpha$ -synuclein cause familial early onset Parkinson's disease suggesting that Lewy bodies contribute mechanistically to the degeneration of neurons in Parkinson's disease (Polymeropoulos *et al.*, *Science* 276:2045-2047, 1997; Kruger *et al.*, *Nature Genet.* 18:106-108, 1998). As described in the literature, *in vitro* studies have demonstrated that recombinant  $\alpha$ -synuclein can form Lewy body-like fibrils (Conway *et al.*, *Nature Med.* 4:1318-1320, 1998; Hashimoto *et al.*, *Brain Res.* 799:301-306, 1998; Nahri *et al.*, *J. Biol. Chem.* 274:9843-9846, 1999). It has been further reported in the literature that  $\alpha$ -synuclein aggregation and fibril formation fulfills the criteria of a nucleation-dependent polymerization process (Wood *et al.*, *J. Biol. Chem.* 274:19509-19512, 1999).

Hence, those of skill in the art are well-aware that  $\alpha$ -synuclein is a therapeutic target for treatment of Lewy body disease and Parkinson's disease. One of skill in the art would further recognize that compounds that prevent, inhibit, disassemble, disrupt and/or disaggregate  $\alpha$ -synuclein fibril, have utility in treatment of Lewy body disease and Parkinson's disease.

**The amount of direction and guidance presented in teachings in the specification**

As described in the application,  $\alpha$ -synuclein recombinant protein, and non-amyloid component (known as NAC-P), which is a 35-amino acid peptide fragment of  $\alpha$ -synuclein, both have the ability to form fibrils when incubated at 37 °C, and are positive with amyloid stains such as Congo red (demonstrating a red/green birefringence when viewed under polarized light) and Thioflavin S (demonstrating positive fluorescence). The application further describes that Parkinson's disease  $\alpha$ -synuclein fibrils, like the A $\beta$  fibrils of Alzheimer's disease, also consist of a predominant beta-pleated sheet structure. Therefore, one of skill in the art would recognize that the compounds found to inhibit, prevent, disassemble, disrupt and/or disaggregate A $\beta$  amyloid fibril are also effective in the inhibition, prevention, disassembly, disruption and/or disaggregation of  $\alpha$ -synuclein fibril.

The specification describes on page 19, lines 7-10, that compounds of the instantly claimed methods act to inhibit or prevent amyloid fibril formation, inhibit or prevent amyloid fibril growth, and/or cause disassembly, disruption, and/or disaggregation of preformed amyloid fibrils and amyloid protein deposits. The exemplary embodiments described in the specification demonstrate disassembly/disruption of A $\beta$  1-42 fibrils, dose-dependent disassembly/disruption

Application S. No. 10/762,444

Filed: January, 21, 2004

Page 13 of 15

of A $\beta$  1-40 fibrils, disaggregation of A $\beta$  1-40 fibrils and dose-dependent disaggregation of A $\beta$  1-40 fibrils by compounds within the scope of the instant claims.

Based on the application disclosure and the exemplary embodiments in the application, one of skill in the art would recognize that the compounds of formula A would have similar activity in prevention, inhibition, disassembly/disruption and disaggregation of  $\alpha$ -synuclein fibril and in treatment of Lewy body disease or Parkinson's disease. Therefore, the application provides sufficient guidance for one of skill in the art to make and use the full scope of the claimed subject matter.

#### **Presence of working examples**

The application provides working examples where disassembly/disruption of A $\beta$  1-42 fibrils and disaggregation of A $\beta$  1-40 fibrils by the compounds used in the instantly-claimed methods is illustrated. Example 1 provides results that demonstrate the disassembly/disruption of A $\beta$  1-42 amyloid fibril as determined by inhibition of Thioflavin T fluorescence by compounds within the scope of claim 4. Example 3 provides results that demonstrate the disaggregation of pre-aggregated A $\beta$  1-40 amyloid fibril as determined by Congo red spectrophotometric assay. As described in the application,  $\alpha$ -synuclein fibrils, like the A $\beta$  fibrils of Alzheimer's disease, also consist of a predominant beta-pleated sheet structure. Therefore, one of skill in the art would recognize that the compounds found to disassemble, disrupt and disaggregate A $\beta$  amyloid fibril would also be effective in disassembly/disruption and disaggregation of  $\alpha$ -synuclein fibrils and in treatment of Lewy body disease or Parkinson's disease.

#### **Conclusion**

In light of the scope of the claims, the description in the application, the high level of skill of those in this art, and the extensive knowledge of those of skill in this art, it would not require undue experimentation to practice full scope of the claims.

Examiner is reminded that applicant is entitled to claims that are commensurate in scope not only with what applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicant has disclosed. As discussed above, the specification discloses the use of compounds of formula A in disassembly/disruption and disaggregation of A $\beta$  amyloid fibril and describes that the

Application S. No. 10/762,444

Filed: January, 21, 2004

Page 14 of 15

compounds would be similarly effective in the inhibition, prevention, disassembly, disruption and/or disaggregation of  $\alpha$ -synuclein fibril. Based on the literature, those of skill in the art are well-aware that  $\alpha$ -synuclein is as a therapeutic target for treatment of Lewy body disease and Parkinson's disease. Therefore, based upon the disclosure in the application, those skilled in the art can practice the methods within the scope of instant claims.

**REJECTION OF CLAIMS 1-11 UNDER 35 U.S.C. §102(b)**

Claims 1-11 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Saeed *et al.* (U.S. Patent 3,833,732). The Office Action alleges that Saeed teaches the use of gallic acid in a pharmaceutical formulation for the treatment of inflammation. The Office Action further alleges that the reference also discloses that gallic acid is used for boosting the anti-parkinson activity of L-DOPA. Reconsideration of the grounds for this rejection is respectfully requested in view of the following remarks.

**Instant claims 1-11**

Claim 1 recites a drug product for the treatment of amyloidosis in a mammal suffering therefrom, comprising a container labeled or accompanied by a label indicating that the drug product is for the treatment of amyloidosis, the container containing one or more dosage units each comprising at least one pharmaceutically acceptable excipient and, as an active ingredient, an isolated pure compound of formula A. Claims 2 and 3 further describe the drug product of claim 1. Claims 4-6 and 8 are directed to methods of treating Lewy body disease or Parkinson's disease characterized by alpha-synuclein fibril formation, by administration a therapeutically effective amount of an isolated pure compound of formula A. Claim 9 recites a drug product for the treatment of Lewy body disease or Parkinson's disease in a mammal suffering therefrom, comprising a container labeled or accompanied by a label indicating that the drug product is for the treatment of Lewy body disease or Parkinson's disease, the container containing one or more dosage units each comprising at least one pharmaceutically acceptable excipient and, as an active ingredient, an isolated pure compound of formula A. Claims 10 and 11 further describe the drug product of claim 9.

**Disclosure of Saeed *et al.* and differences from the instant claims**

Saeed *et al.* discloses that gallic acid and its alkyl ester are used for boosting the anti-parkinson activity of L-DOPA. As discussed above, the drug products and methods of the

Application S. No. 10/762,444

Filed: January, 21, 2004

Page 15 of 15

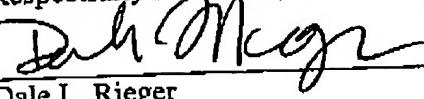
instant claims encompass compounds of formula A. Applicants respectfully submit that gallic acid and its esters are not with the scope of the instant claims. Therefore, Saeed *et al.* does not anticipate claims 1-11. Applicants request reconsideration and removal of the rejection.

\*\*\*\*\*

In view of the above, allowance of the application is respectfully requested.

The Commissioner is hereby authorized to charge any required fee(s) to Jones Day

Deposit Account No. 50-3013.

Date:	June 2, 2006	Respectfully submitted, 	43,045
		Dale L. Rieger	(Reg. No.)
		JONES DAY 222 East 41st Street New York, New York 10017 858.314.1200	

CJD-528239v2

PAGE 16/18 \* RCVD AT 6/2/2006 5:05:27 PM [Eastern Daylight Time] \* SVR:USPTO-EFXRF-5/21 \* DNIS:2738300 \* CSID:+8583141151 \* DURATION (mm:ss):04:50